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(5) If known

Application code No.	Representative code No.	Delivery address code No.

(6) Description of the invention (*if too long, submit on a separate sheet in 3 copies*)
Epothilone Derivatives and their use

(7) See explanations and cost information on the reverse side

Other applications
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3. — summary (optionally with drawings fig. ___)
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(12) (Dr. Meyer)

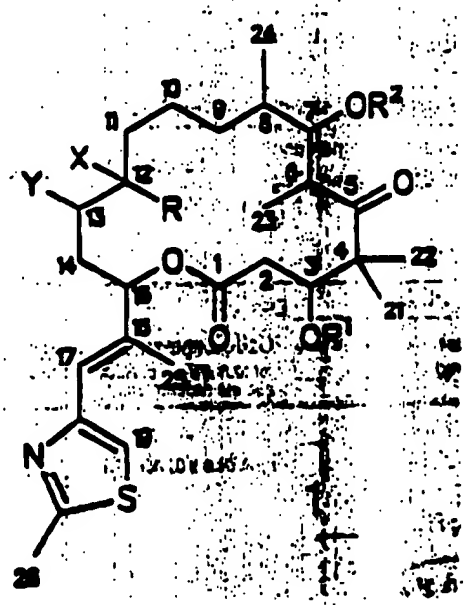
DE 195 42 986.9

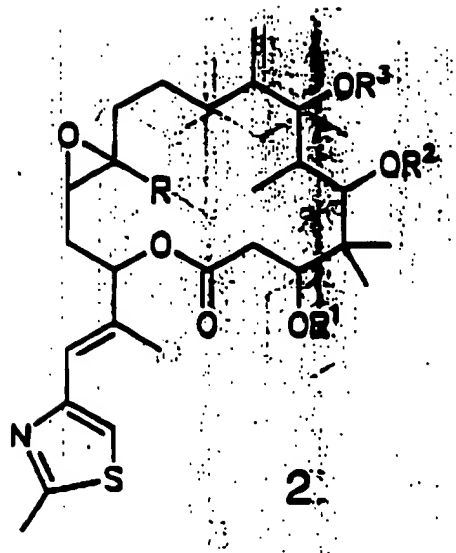
November 17, 1995/pl

Our reference: 7865

EPOTHILONE DERIVATIVES AND THEIR USE

The present invention concerns general epothilone derivatives and their use for the production of drugs. Especially, the present invention is concerned with the preparation of epothilone derivatives according to the general Formulas 1 to 7 given below, as well as with their use for the production of therapeutic agents and agents for plant protection.





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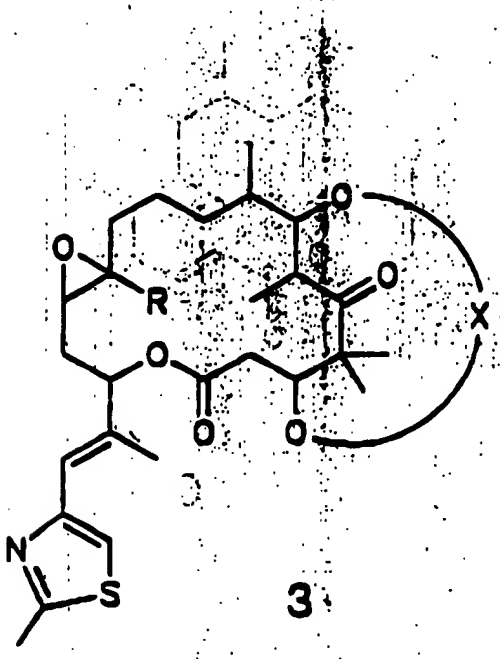

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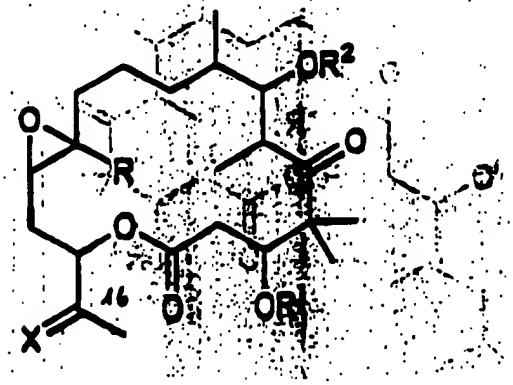

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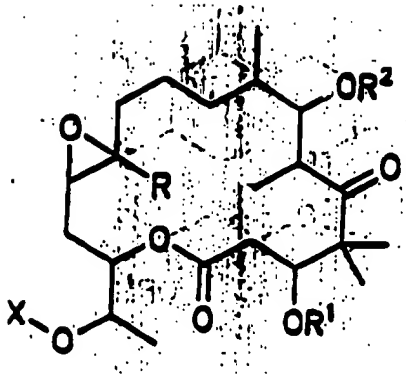

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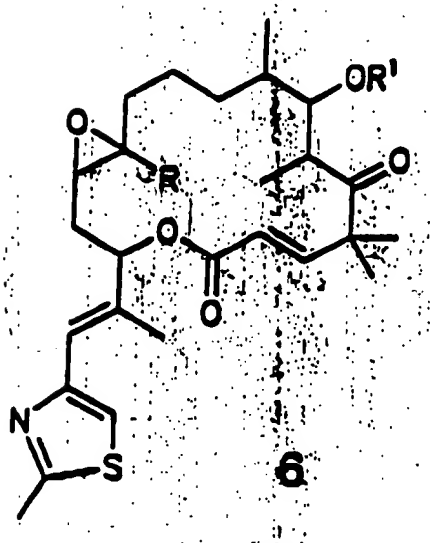

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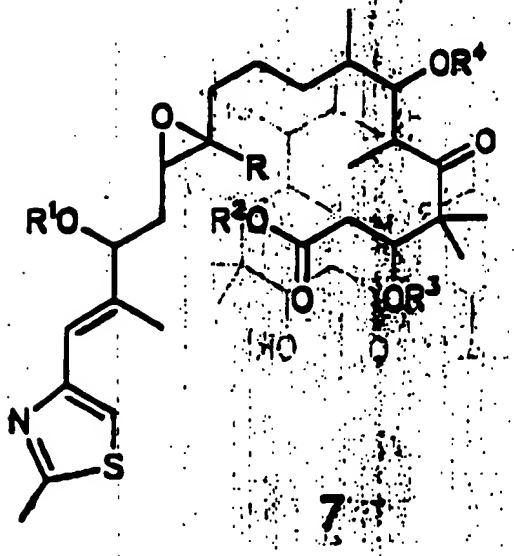

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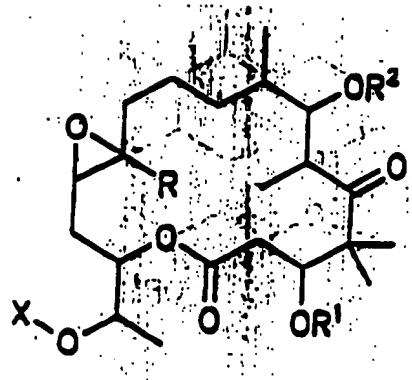

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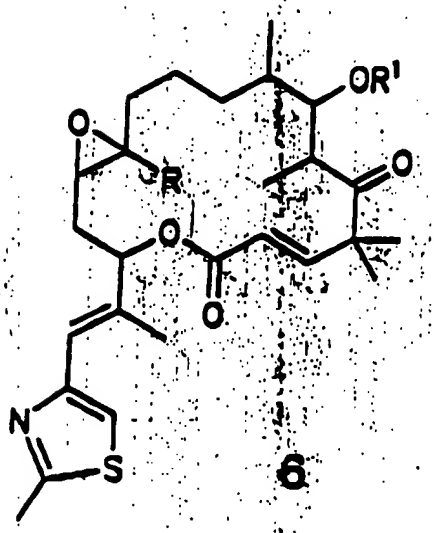

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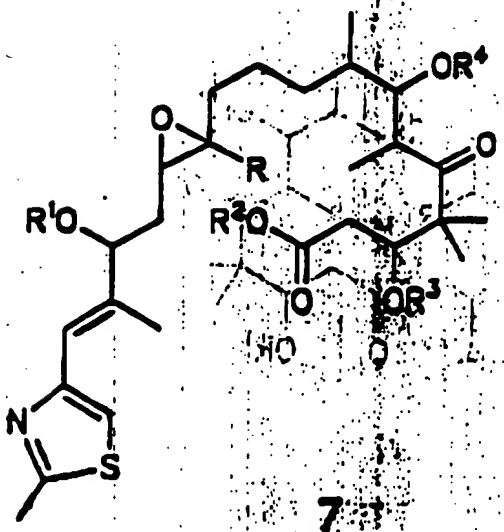


7

In the above **Formulas 1 to 7**, the symbols have the following meanings:

R = H, C_{1-4}-alkyl;
R^1, R^2, R^3, R^4, R^5 = H, C_{1-6}-alkyl,
C_{1-6}-acyl-benzoyl,
C_{1-4}-trialkylsilyl,
benzyl,
phenyl,
C_{1-6}-alkoxy-,
C_6-alkyl-, hydroxy and halogen-substituted benzyl or phenyl;
also, two of the groups R^1 to R^5 may be combined to form the grouping $-(CH_2)_n-$ with n = 1 to 6 and the alkyl or acyl groups contained in the groups are either straight-chain or branched groups.

In **Formula 1**, X and Y are either identical or different and can stand for halogens, OH, O-(C_{1-6})-acyl, O-(C_{1-6})-alkyl, O-benzoyl.

In **Formula 3**, X generally stands for -C(O)-, -C(S)-, -S(O)-, $-CR^1R^2-$, where R^1 and R^2 have the meaning given above and $-SiR_2-$, where R has the meaning given above.

In **Formula 4**, X stands for oxygen, NOR^3, $N-NR^4R^5$, and $N-NHCONR^4R^5$, where the groups R^3 to R^5 have the meaning given above.

In **Formula 5**, X stands for hydrogen, C_{1-18}-alkyl, C_{1-18}-acyl, benzyl, benzoyl and cinnamoyl.

Compounds according to general **Formula 1** are accessible starting from epothilone A and B, as well as from their 3-O- and/or 7-O-protected derivatives by opening the 12,13-epoxide. When hydrogen halides are used for this purpose in a preferred nonaqueous solvent, the halohydrins X = Hal, Y = OH and Y = OH, Y = Hal are obtained. Protonic acids, for example, toluenesulfonic acid and trifluoroacetic acid, lead to 12,13-diols in the presence of water and then these are acylated subsequently according to standard methods (for example, with carboxylic acid anhydrides and pyridine or triethylamine/DMAP) or are alkylated (alkyl

halides and silver oxide). For this purpose, the 3- and 7-hydroxy groups can be protected temporarily as the formate (cleaved with NH_3/MeOH) or p-methoxybenzyl ether (cleaved with DDQ).

Compounds according to general **Formula 2** are obtainable from epothilone A and B as well as from their 3-O- and/or 7-O-protected derivatives by reduction, for example, with $NaBH_4$ in methanol. If the 3-OH and/or 7-OH groups are protected reversibly during this process, after acylation or alkylation, and removal of the protecting groups, 5-O-monosubstituted, 3,5- or 5,7-O-disubstituted derivatives according to general **Formula 2** can be obtained.

Reactions of epothilone A and B with bifunctional electrophilic reagents, such as (thio)phosgene, (thio)carbonyldimidazole [sic], thionyl chloride or dialkylsilyl dichlorides or bistriflates give compounds having general **Formula 3**. The bases used as aids here can be pyridine, trialkylamine, optionally together with DMAP or 2,6-lutidine in an aprotic solvent. The 3,7-acetals having general **Formula 3** are formed by transacetalization, for example, of dimethylacetals, in the presence of an acidic catalyst.

Compounds according to general **Formula 4**, obtained from epothilone A and B or from their 3-O- and/or 7-O-protected derivatives by ozonolysis and reductive processing, for example, with dimethyl sulfide. The C-16 ketones can then be converted to the oximes, hydrazones or semicarbazones according to standard methods known to the expert in the field. Furthermore, they are converted into C-16/C-17 olefins by the Wittig, Wittig-Horner, Julia or Petersen olefination method.

The 16-hydroxy derivatives according to general **Formula 5** are obtainable by reduction of the C-16 keto group, for example, with aluminum hydride or borohydride. When the 3-OH and 7-OH groups are protected correspondingly, they can be acylated or alkylated selectively. The liberation of the 3-OH- and 7-OH groups is done, for example, with NH_3/MeOH in the case of O-formyl and with DDQ in the case of O-p-methoxybenzyl.

The compounds having general **Formula 6** are obtained from derivatives of epothilone A and B in which the 7-OH group is protected by acyl or ether groups, in which the 3-OH group

is, for example, formylated, mesylated or tosylated and then eliminated by treatment with a base, for example, DBU. The 7-OH group can be liberated as described above.

Compounds having general **Formula 7** are obtained from epothilone A and B or from their 3-OH- and 7-OH-protected derivatives by basic hydrolysis, for example, with NaOH in MeOH. After protection of the 19-OH group, the carboxyl group can be converted to the ester by alkylation with diazoalkanes.

Furthermore, the invention is concerned with means for plant protection in agriculture, forestry and/or gardening, consisting of one or several of the epothilone derivatives described above or consisting of one or several of the epothilone derivatives described above in addition to one or several of the usual carrier(s) and/or diluent(s).

Finally, the invention is concerned with therapeutic agents, consisting of one or several of the compounds listed above or of one or several of the compounds listed above in addition to one or several of the usual carrier(s) and/or diluent(s). These agents can exhibit especially cytotoxic activities and/or cause immune suppression, so that they can especially preferably be used as cytostatic agents.

The invention is explained further and described by the description of a few selected practical examples.

Examples

Translator's note: In the infrared spectra in the examples, the general English abbreviations are used, s, m, w, vs, b, etc., except for Sch = shoulder and ny = ν (nu) Also, the abbreviation lg stands for log.

Compound 1a

20 mg (0.041 mmole) of epothilone A is dissolved in 1 mL of acetone, with 50 µL (0.649 mmole) of trifluoroacetic acid is added and the mixture is stirred overnight at 50°C. For work-up, the reaction mixture is treated with 1 M pH 7 phosphate buffer and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed. The purification of the crude product is done with the aid of preparative layer-chromatography (solvent: dichloromethane/acetone, 85:15).

Yield: 4 mg (19%) isomer I
4 mg (19%) isomer II

Isomer I

R_f (dichloromethane/acetone, 85:15): 0.46

IR (Film): ν = 3440 (m, b, Sch), 2946 (s, Sch), 1734 (vs), 1686 (m), 1456 (m), 1375 (w), 1256 (s, Sch), 1190 (w, b, Sch), 1071 (m, Sch), 884 (w), 735 (w) cm^{-1}.

MS (20/70 eV): m/e (%) = 493 (43 $[M-H_2O]^+$), 394 (47), 306 (32), 206 (30), 181 (40), 166 (72), 139 (100), 113 (19), 71 (19), 57 (24), 43 (24).

High resolution: $C_{26}H_{39}O_6NS$ calculated: 493.2498 for $[M-H_2O]^+$
found: 493.2478

Isomer II

R_f (dichloromethane/acetone, 85:15): 0.22

IR (Film): ν = 3484 (s, b, Sch), 2942 (vs, Sch), 1727 (vs), 1570 (w), 1456 (m), 1380 (m), 1265 (s), 1190 (w), 1069 (m), 975 (w), cm^{-1}.

MS (20/70 eV): m/e (%) = 493 (21, $[M-H_2O]^+$), 394 (12), 306 (46), 206 (37), 181 (63), 166 (99), 139 (100), 113 (21), 71 (23), 57 (33), 43 (28).

High resolution: $C_{26}H_{39}O_6NS$ calculated: 493.2498 for $[M-H_2O]^+$
found: 493.2475

Compound 1b

Epothilone A, 55 mg (0.111 mmole), is dissolved in 0.5 mL of tetrahydrofuran, 0.5 mL of 1 N hydrochloric acid is added and the mixture is stirred for 30 minutes at room temperature. Then 1 N phosphate buffer of pH 7 is added and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed. The purification of the crude product is done with the aid of preparative layer chromatography (solvent: dichloromethane/methanol, 90:10).

Yield 1c: 19 mg (32%).

R_f (dichloromethane/methanol, 90:10): 0.46

IR (Film): $\tilde{\nu}$ = 3441 (s, br, Sch), 2948 (s, Sch), 1725 (vs, Sch), 1462 (m), 1381 (w), 1265 (m), 1154 (w), 972 (m, br, Sch) cm^{-1}.

UV (Methanol): λ_{max} (lg ϵ) = 210 (4.29), 248 (4.11) nm.

MS (20/70 eV): m/e (%) = 529 (30 [M+]), 494 (10), 342 (38), 306 (23), 194 (32), 164 (100), 140 (31), 113 (15), 57 (16).

High resolution: $C_{26}H_{40}O_6ClNS$ calculated: 529.2265 for [M^+],
found: 529.2280

Compound 1c

12-Chloro-13-hydroxy-epothilone A (1b), 25 mg (0,047 mmole), is dissolved in 1 mL of dichloromethane, and then 29 mg (0.235 mmole) of dimethylaminopyridine, 151 µL (1.081 mmole) of triethylamine and 20 µL (0.517 mmole) of 98% formic acid are added. The reaction mixture is cooled with ice/sodium chloride. After reaching -15°C, 40 µL (0.423 mmole) of acetic anhydride is added to the reaction mixture, followed by stirring for 70 minutes at -15°C. Since the thin-layer chromatogram did not show complete conversion, another 6 mg (0.047 mmole) of dimethylaminopyridine, 7 µL (0.047 mmole) of triethylamine, 2 µL of 98% formic acid (0.047 mmole) and 4 µL (0.047 mmole) of acetic anhydride are added to the reaction mixture, followed by stirring for 60 minutes.

For work-up, the reaction mixture is heated to room temperature, 1 M phosphate buffer with pH 7 is added and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed.
The purification of the crude product is done with the aid of preparative layer chromatography (solvent: dichloromethane/acetone, 90:10).
Yield: 5 mg (18%).

Compound 1c

R_f (Dichloromethane/acetone, 90-10): 0.67

IR (Film): $\tilde{\nu}$ = 3497 (w, b, Sch), 2940 (s, b, Sch), 1725 (vs), 1468 (m, b, Sch), 1379 (m), 1265 (s), 1253 (s), 1175 (vs), 972 (m, b, Sch), 737 (s) cm^{-1}.

MS (20/70 eV): m/e (%) = 613 (9 [M^+]), 567 (43), 472 (63), 382 (23), 352 (21), 164 (100), 151 (33), 96 (31), 69 (17), 44 (26).

High resolution: $C_{29}H_{40}O_9NSCl$ calculation: 613.2112 for [M^+]
found: 613.2131

Compound 1d

10 mg (0.020 mmole) of epothilone B is dissolved in 0.5 mL of tetrahydrofuran, then 0.5 mL of 1 N hydrochloric acid is added and the mixture stirred for 30 minutes at room temperature. Then 1 M phosphate buffer at pH 7 is added and the aqueous phase is extracted 4 times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed.

The purification of the crude product is done with the aid of preparative layer chromatography (solvent: dichloromethane/acetone, 85:15).
Yield: 1 mg (9%)

R_f (Dichloromethane/acetone, 85:15): 0.38

MS (20/70 eV): m/e (%) = 543 (3 [M⁺]), 507 (14), 320 (19), 234 (95), 194 (17), 182 (23), 164 (100), 140 (22), 113 (14), 71 (13).

High resolution: $C_{27}H_{42}O_6NSCl$ calculated: 543.2421 for [M^+]
found: 543.2405

Compound 2a

Epothilone A, 100 mg (0.203 mmole), is dissolved in 4 mL of tetrahydrofuran/1 M phosphate buffer, pH 7 (1:1) and sodium borohydride (150 mg = 3.965 mmole) is added until the thin-layer chromatogram shows that the starting material reacted completely. Then the mixture is diluted with 1 M phosphate buffer, pH 7 and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed.

The purification of the crude product is done by silica gel chromatography (solvent: dichloromethane/acetone, 95:5 - in 5 steps to dichloromethane/acetone, 85:15).
Yield: (20%)

R$_f$ (Dichloromethane/acetone, 75:25): 0.27

IR (Film): $\tilde{\nu}$ = 3413 (s, b, Sch), 2965 (vs, Sch), 1734 (vs), 1458 (m, b, Sch), 1383 (m, Sch), 1264 (s, b, Sch), 1184 (m, b, Sch), 1059 (s, Sch), 966 (s), 885 (w), 737 (m) cm^{-1}

MS (20/70 eV): m/e (%) = 495 (6 [M$^+$]), 477 (8), 452 (12), 394 (9), 364 (16), 306 (49), 194 (19), 178 (35), 164 (100), 140 (40), 83 (21), 55 (27).

High resolution: $C_{25}H_{41}O_6NS$ calculated: 495.2655 for [M$^+$]
found: 495.2623

Compound 3a-d (a-d are stereoisomers)

Epothilone, 100 mg (0.203 mmole) is dissolved in 3 mL of pyridine, with 50 µL (0.686 mmole) of thionyl chloride added and the mixture is stirred for 15 minutes at room temperature. Then, 1 M phosphate buffer, pH 7, is added and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed. The purification of the crude product and separation of the four stereoisomers 3a-d is done with the aid of preparative layer chromatography (solvent: toluene/methanol, 90:10).

Compound 3a

Yield: 4 mg (12%)

R_f (toluene/methanol, 90:10): 0.50

IR (Film): ν = 2961 (m, b, Sch), 1742 (vs), 1701 (vs), 1465 (m, Sch), 1389 (m, Sch), 1238 (s, Sch), 1210 (vs, Sch), 1011 (s, Sch), 957 (s, b, Sch), 808 (m, Sch), 768 (s, Sch) cm^{-1}.

UV (Methanol): λ_{max} (lg ϵ) = 210 (4.50), 248 (4.35) nm.

MS (20/70 eV): m/e (%) = 539 (40 [M^+]), 457 (22), 362 (16), 316 (27), 222 (30), 178 (30), 164 (100), 151 (43), 96 (38), 69 (29), 55 (28), 43 (20).

High resolution: $C_{26}H_{37}O_7NS_2$ calculated: 539.2011 for [M^+]

Compound 3b

Yield: 14 mg (13%)

R_f (toluene/methanol, 90:10): 0.44

IR (Film): ν = 2963 (s, br, Sch), 1740 (vs), 1703 (s), 1510 (w), 1464 (m, br, Sch), 1389 (m, Sch), 1240 (s, br, Sch), 1142 (m), 1076 (w), 1037 (w), 1003 (m), 945 (s, br, Sch), 806 (m, Sch), 775 (s), 737 (m) cm^{-1}.

UV (Methanol): λ_{max} (lg ϵ) = 211 (4.16), 250 (4.08) nm.

MS (20/70 eV): m/e (%) = 539 (27 [M^+]), 475 (17), 322 (41), 306 (67), 222 (16), 206 (17), 194 (19), 178 (32), 164 (100), 151 (33), 125 (18), 113 (15), 96 (39), 81 (23), 64 (58), 57 (42), 41 (19).

High resolution: $C_{26}H_{37}O_7NS_2$ calculated: 539.2011 for [M^+]
found: 539.1998

Compound 3c

Yield: 4 mg (4%)

R_f (toluene/methanol, 90:10): 0.38

MS (20/70 eV): m/e (%) = 539 (68) [M^+], 322 (22), 306 (53), 222 (36), 178 (31), 164 (100), 151 (41), 96 (25), 81 (20), 69 (26), 55 (25), 41 (25):

High resolution: $C_{26}H_{37}O_7NS_2$ calculated: 539.2011 for [M^+]
found: 539.2001

Compound 3d

Yield: 1 mg (1%)

R_f (toluene/methanol, 90:10): 0.33

MS (20/70 eV): m/e (%) = 539 (68) [M^+], 322 (35), 306 (51), 222 (41), 178 (31), 164 (100), 151 (46), 96 (31), 81 (26), 69 (34), 55 (33), 41 (35).

High resolution: $C_{26}H_{37}O_7NS_2$ calculated: 539.2011 for [M^+]
found: 539.1997

Compound 4a

Epothilone A, 10 mg (0.020 mmole), is dissolved in 2 mL of dichloromethane, cooled to -70°C and then treated with ozone for 5 minutes until a weak blue coloration develops. The resulting reaction mixture is then treated with 0.5 mL of dimethyl sulfide and heated to room temperature. In the work-up, the solvent is removed from the reaction mixture and finally the product is purified with preparative layer chromatography (solvent: dichloromethane/acetone/methanol, 85:10:5).

Yield: 5 mg (64%)

R_f (Dichloromethane/acetone/methanol, 85:10:5): 0.61

IR (Film): $\tilde{\nu}$ = 3468 (s, br, Sch), 2947 (s, br, Sch), 1734 (vs, Sch), 1458 (w), 1380 (w), 1267 (w), 1157 (w), 1080 (w), 982 (w) cm^{-1}.

UV (Methanol): λ_{max} (lg ε) = 202 (3.53) nm.

MS (20/70 eV): m/e (%) = 398 (2 [M⁺]), 380 (4), 267 (14), 249 (17), 211 (20), 193 (26), 171 (34), 139 (34), 111 (40), 96 (100), 71 (48), 43 (50).

High resolution: $C_{21}H_{34}O_7$ calculated: 398.2305 for [M⁺]
found: 398.2295

Compound 6a

3,7-Di-O-formyl-epothilone A, 10 mg (0.018 mmole), is dissolved in 1 mL of dichloromethane, 27 µL (0.180 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is added and the mixture stirred at room temperature for 60 minutes.

For work-up, the reaction mixture is treated with 1 M sodium dihydrogen phosphate buffer, pH 4.5, and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed.

After elimination of the solvent, the resulting crude product is dissolved in 1 mL of methanol, treated with 200 µL of ammoniacal methanol solution (2 mmole of NH_3/mL of methanol) and stirred overnight at room temperature. For work-up, the solvent is removed in vacuum.

Yield: 4 mg (22%)

R_f (Dichloromethane/acetone, 85:15): 0.46

IR (Film): ν = 3445 (w, br, Sch), 2950 (vs, br, Sch), 1717 (vs, Sch), 1644 (w), 1466 (m, Sch), 1370 (m, Sch), 1267 (s, br, Sch), 1179 (s, Sch), 984 (s, Sch), 860 (w), 733 (m) cm^{-1}.

UV (Methanol): λ_{max} (lg ε) = 210 (4.16) nm.

MS (20/70 eV): m/e (%) = 475 (28 [M⁺]), 380 (21), 322 (37), 318 (40), 304 (66), 178 (31), 166 (100), 151 (29), 140 (19), 96 (38), 81 (20), 57 (26).

High resolution: $C_{26}H_{37}O_5NS$ calculated: 475.2392 for [M^+]
found: 475.2384

[1]

Compound 6b

3,7-Di-O-formyl-epothilone A, 50 mg (0.091 mmole), is dissolved in 1 mL of dichloroethane, 2 mL (0.013 mole) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is added and the mixture stirred for 12 hours at 90°C.

For work-up, the reaction mixture is treated with 1 M sodium dihydrogen phosphate buffer, pH 4.5, and the aqueous phase extracted four times with ethyl acetate. The combined

[1] [Note: Compound 5 was not mentioned in the original. It jumps from 4 to 6.]

For work-up, the reaction mixture is treated with 1 M sodium dihydrogen phosphate buffer, pH 4.5, and the aqueous phase extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent removed.

The purification of the crude product, which consists of two compounds, is done with the aid of preparative layer chromatography (solvent: dichloromethane/acetone, 90:10).
Yield: 7 mg (15%)

Substance code
R_f (Dichloromethane/acetone, 90:10): 0.62

IR (Film): ν = 2951 (m, br, Sch), 1723 (vs), 1644 (w, br, Sch), 1468 (w), 1377 (w), 1271 (m, br, Sch), 1179 (s), 987 (m, br, Sch), 735 (w, br, Sch) cm^{-1}.

UV (Methanol): λ_{max} (lg ϵ) = 210 (4.44) nm.

MS (20/70 eV): m/e (%) = 503 (68 [M^+]), 408 (58), 390 (32), 334 (25), 316 (34), 220 (21), 206 (27), 194 (20), 181 (33), 164 (100), 151 (34), 139 (28), 113 (20), 96 (82), 81 (33), 67 (24), 55 (26), 43 (22).

High resolution: $C_{27}H_{37}O_6NS$ calculated: 503.2342 for [M^+]
found: 503.2303

Compound 6c
3,7-Di-O-acetyl-epothilone, 5 mg (0.009 mmole), is dissolved in 1 mL of methanol, 150 µL of an ammoniacal methanol solution (2 mmole of NH_3/mL of methanol) is added and the mixture stirred overnight at 50°C.

For work-up, the solvent is removed in vacuum and the crude product is purified with the aid of preparative layer chromatography (solvent: toluene/methanol, 90:10).

Yield: 3 mg (67%)

R_f (Dichloromethane/acetone, 90:10): 0.55

IR (Film): ν = 2934 (s, b, Sch), 1719 (vs, b, Sch), 1641 (m), 1460 (m, Sch), 1372 (s, Sch), 1237 (vs, b, Sch), 1179 (s, Sch), 1020 (s), 963 (s, Sch), 737 (vs) cm^{-1}.

UV (Methanol): λ_{max} (lg ϵ) = 210 (4.33) nm.

MS (20/70 eV): m/e (%) = 517 (57 [M$^+$]), 422 (58), 318 (31), 194 (20), 181 (34), 166 (100), 151 (31), 96 (96), 81 (32), 69 (27), 55 (29), 43 (69).

High resolution: $C_{28}H_{39}O_6NS$ calculated: 517.2498 for [M$^+$]
found: 517.2492

Compound 7a

Epothilone, 20 mg (0.041 mmole), is dissolved in 0.5 mL of methanol, 0.5 mL of 1 N sodium hydroxide is added and the mixture stirred for 5 minutes at room temperature.

For work-up, the reaction mixture is treated with 1 M phosphate buffer, pH 7, and the aqueous phase is extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and the solvent is removed. The purification of the crude product is done with the aid of preparative layer chromatography. (Solvent: dichloromethane/methanol, 85:15).

Yield: 11 mg (52%)

R_f (Dichloromethane/methanol, 85:15): 0.92

IR (Film): ν = 3438 (s, br, Sch), 2971 (vs, br, Sch), 1703 (vs), 1507 (m), 1460 (s, Sch), 1383 (m, Sch), 1254 (w), 1190 (w, br, Sch), 1011 (w, br, Sch), 866 (w, br), 729 (s) cm^{-1}.

MS (20/70 eV): m/e (%) = 423 (0.1 [M$^+$]), 323 (4), 168 (89), 140 (100), 85 (31), 57 (67).

High resolution: $C_{23}H_{37}O_4NS$ calculated: 423.2443 for [M$^+$]
found: 423.2410

Compound 7b

5 mg (0.009 mmole) of 7-O-acetyl-epothilone is dissolved in 1 mL of methanol, 200 µL of an ammoniacal methanol solution (2 mmole of NH_3/mL of methanol) is added and the mixture is stirred for 2 days at 50°C. For work-up, the solvent is removed in vacuum. The purification of the crude product is done with the aid of preparative layer chromatography (solvent: toluene/methanol, 90:10).

Yield: 3 mg (59%)

R_f (Dichloromethane/methanol, 90:10): 0.63

IR (Film): ν = 3441 (m, b, Sch), 2946 (s, Sch), 1732 (vs), 1600 (w), 1451 (m), 1375 (m), 1246 (s, b, Sch), 1013 (m, b, Sch) cm^{-1}.

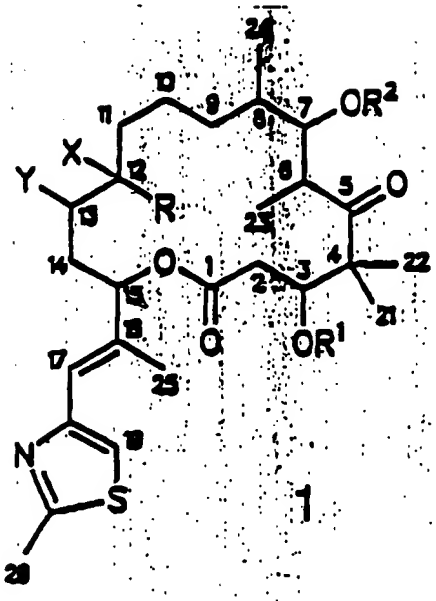
UV (Methanol): λ_{max} (lg ε) = 211 (3.75), 247 (3.59) nm.

MS (20/70 eV): m/e (%) = 567 (1 [M$^+$]), 465 (4), 422 (7), 388 (5), 194 (5), 182 (7), 168 (65), 164 (17), 140 (100), 97 (10), 71 (22), 43 (27).

High resolution: $C_{29}H_{45}O_5NS$ calculated: 567.2866 for [M$^+$]
found: 567.2849

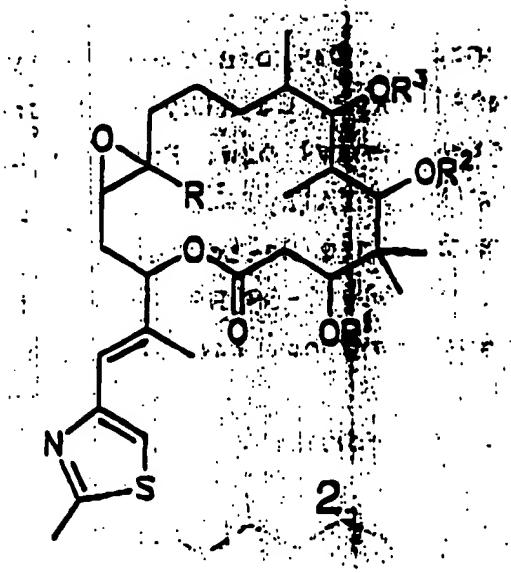
Patent Claims

1. Epothilone derivative having Formula 1



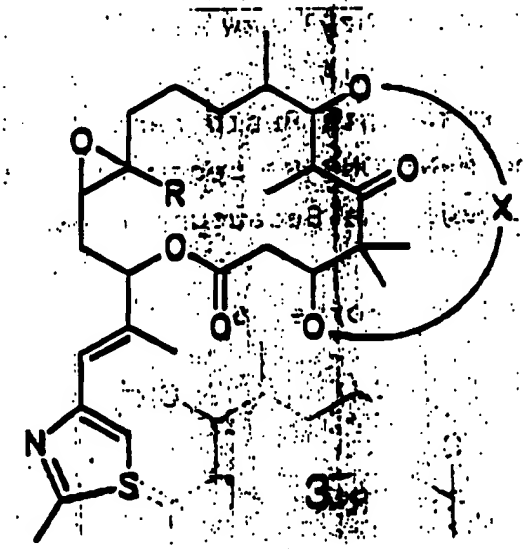
where R = H, C_{1-4}-alkyl; R^1, R^2 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; and the alkyl and acyl groups in these groups are straight-chain or branched groups and X and Y are either the same or different and stand for halogen, OH, O-(C_{1-6})-acyl, O-(C_{1-6}-alkyl or O-benzoyl).

2. Epothilone derivative having formula 2



where R = H, C_{1-4}-alkyl; R^1, R^2, R^3 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; the alkyl and acyl groups contained in these groups are straight-chain or branched groups.

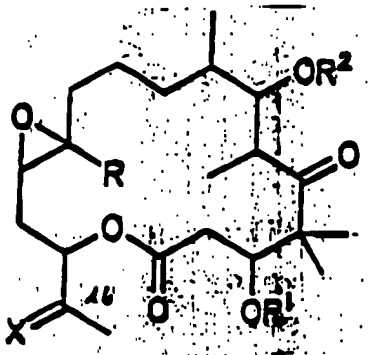
3. Epothilone derivative according to formula 3



where R = H, C_{1-4}-alkyl; R^1, R^2 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy-, and halogen-substituted benzyl and phenyl;

the alkyl and acyl groups contained in these groups are straight-chain or branched groups and X stands generally for -C(O)-, -C(S)-, -S(O)-, $-CR^1R^2-$ and $-SiR_2-$, where R, R^1 and R^2 have the meaning given above.

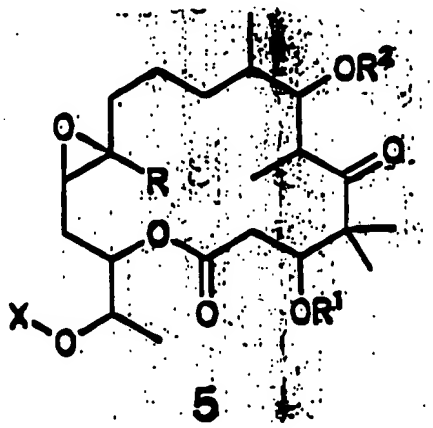
4. Epothilone derivative according to formula 4



4

where R = H, C_{1-6}-alkyl; R^1, R^2, R^3, R^4, R^5 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; the alkyl and acyl groups contained in these groups are straight-chain or branched groups; X stands for oxygen, NOR^3, $N\text{-}NR^4R^5$, and $N\text{-}NHCONR^4R^5$, where the groups R^3 to R^5 have the meaning given above.

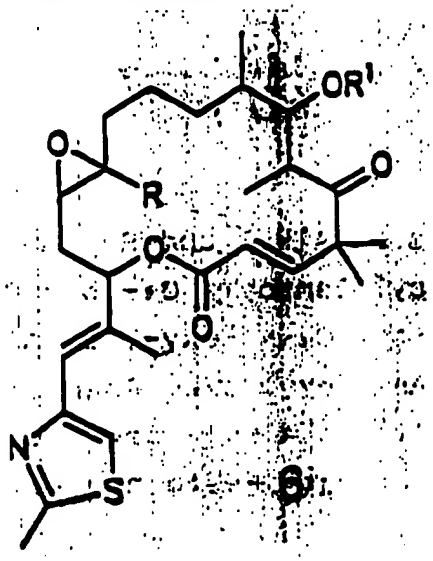
5. Epothilone derivative having formula 5



5

where R = H, C_{1-4}-alkyl; R^1, R^2 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; the alkyl and acyl groups contained in these groups are straight-chain or branched groups and X stands for hydrogen, C_{1-18}-alkyl, C_{1-18}-acyl, benzyl, benzoyl and cinnamoyl.

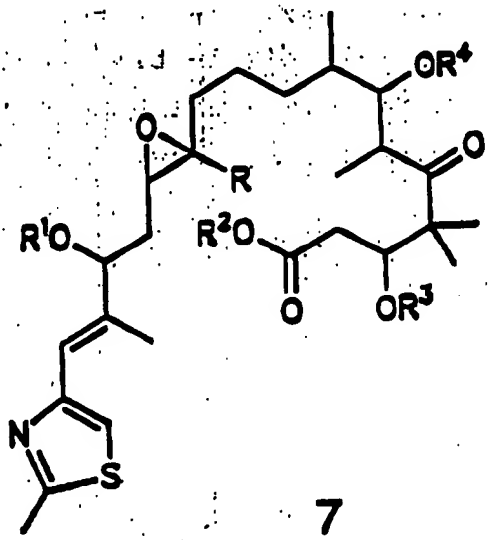
6. Epothilone derivative according to formula 6



6

in which R = H, C_{1-4}-alkyl and R^1 = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; the alkyl and acyl groups contained in these groups are straight-chain or branched groups.

7. Epothilone derivative according to formula 7



7

in which R = H, C_{1-4}-alkyl; and R^1, R^2, = H, C_{1-6}-alkyl, C_{1-6}-acyl, benzoyl, C_{1-4}-trialkylsilyl, benzyl, phenyl, C_{1-6}-alkoxy-, C_6-alkyl-, hydroxy- and halogen-substituted benzyl or phenyl; the alkyl and acyl groups contained in these groups are straight-chain or branched groups.

8. Means for plant protection in agriculture and forestry and/or in gardening, consisting of one or several of the compounds according to one of the previous Claims, or according to one or several of these compounds together with one or several usual carrier(s) and/or diluent(s).

9. Therapeutic agent, especially for use as cytostatic agent, consisting of one or several of the compounds according to one or several of Claims 1 to 7, or one or several compounds according to one or several of Claims 1 to 7 together with one or several of the usual carrier(s) and/or diluent(s).

Summary

The present invention is concerned with epothilone derivatives and their application.